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Original Article

INFLUENCE OF BINDING SOLUTION CONCENTRATION, DRYING DURATION AND DRYING TEMPERATURE ON PHYSIOCHEMICAL PERFORMANCE OF NORFLOXACIN GRANULES AND TABLETS

ZUHAEIR OSMAN*, NEMAT S. ADAM, HASSAN A. HASSAN, ABUBAKR O. NUR

Department of Pharmaceutics, Faculty of Pharmacy, University of Khartoum, Sudan
Email: azuheir@yahoo.com

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ABSTRACT

Objective: To investigate the possible individual and joined influences that binding solution concentration, drying temperature and drying duration might have on the physiochemical attributes of granules and tablets using norfloxacin as a model drug.

Methods: According to implemented 2^3 central composite designs, each of the investigated variables were examined at 5 different levels through different 16 formulation runs. For each formulation, obtained granules were qualified for their bulk density, tap density, Hausner ratio, percent of fine and drug content properties whereas the respective tablets were evaluated for their weight variation, drug content, friability, hardness, disintegration, and drug dissolution attributes.

Results: Indicated that concentration of binder solution, as compared to drying temperature and drying duration, measured more profound influences on granules' tap density, Hausner ratio, % fine and drug content either through its individual linear and quadratic effects or through its joint effect with drying durations ($p<0.05$ at 95% CI for all influences). Whilst tablets' friability appeared to be noticeably influenced by the three investigated variables (P ranged 0.001-0.017 at 95% CI), tablets' hardness and disintegration were found to be considerably affected only by binder solution concentration ($p = 0.001$ and 0.082 at 95% CI, respectively). Moreover, none of the investigated variables has measured a significant influence on tablets' drug content or drug dissolution properties.

Conclusion: The study concluded that quadratic and joint influences of variables on attributes of granule and tablet formulations shouldn't be overlooked and better to be considered in the screening design.

Keywords: Central composite design, Norfloxacin, Granules, Tablets, Joint influences

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INTRODUCTION

One of the difficulties in the quantitative approach for formulation design is the intricacy in understanding the real relationship between causal factors and individual pharmaceutical responses [1, 2]. A knowledgebase can be of most benefit when it consists of scientific and thorough mathematical understanding of the relevant multi-factorial relationships between formulation, process and product quality attributes [3].

Numerous reports have recognized the individual effects of binding solution concentration, drying duration and drying temperature on physiochemical performance of granules and tablets [4-7]. However, the associated joint influences of these variables on properties of yielded granules and tablets have received less consideration among formulation scientists.

The objectives of the present study were to apply 2^3 central composite design in order to explore both the individual and mutual effects of concentration of binder solution, drying temperature and drying duration on the physicochemical properties of yielded granules and tablets using norfloxacin as a model drug.

MATERIALS AND METHODS

Materials

Norfloxacin a pharmaceutical-grade product of Zaheamg Neo Dankong Pharmaceutical Co., Ltd. (China) and was kindly donated by General Medicines Company (GMC, Sudan). Microcrystalline cellulose 101, povidone K30, corn starch, magnesium stearate and sodium starch glycolate were pharmaceutical grade products of Shin Poong Pharm. Co. Ltd. (Korea) and were generously donated by General Medicine Company (GMC, Sudan). Glacial acetic acid and sodium hydroxide pellets were analytical grade products of SD fine-chem (Mumbai) and were made available by Department of Pharmaceutical Chemistry, Faculty of Pharmacy-University of Khartoum. Other materials and reagents were analytical grade obtained from different commercial sources.

Experimental design

Based on the aim of this study, 2^3 central composite design was implemented to generate 16 formulation runs through which 3 variables, namely; concentration of binder solution, drying temperature and drying duration were each examined at 5 levels for their main and interactive influences on the property of produced granules and tablets (table 1).

Preparation of granules and tablets

For different formulation runs, granules and, consequently, tablets were obtained by using wet granulation method in which stated the amount of the model drug (norfloxacin), microcrystalline cellulose (as a filler) and half of the amount of both sodium starch glycolate (as intragranular disintegrant) and starch were mixed for 15 min. The mixed blend was then wetted with hydroalcoholic solution of polyvinyl pyrrolidone of different concentrations (as binding or granulating agent) to form hash mass which was then forced through mesh #8 (2380 µm) and dried in an oven at different temperatures for different time durations. Dried granules were resized using mesh #10 (2000 µm) and divided into two portions for each run. One portion of the granules which contain 60% w/w of norfloxacin was packed in well-closed 50 gm containers and examined for different properties of granules. The second portion of the granules was proceeded into tablets by adding and mixing for 5 min the second half amounts of both sodium starch glycolate (as intergranular disintegrant) and starch followed by addition of magnesium stearate and mixing further for extra 3 min. The final

blend was then compressed using single punch tablet compression machine (Erweka, Germany) equipped with 12-mm flat-faced punch to produce tablets with an average weight of 500 mg and containing 200 mg of loaded drug per unit dosage. Tablets were packed in plastic containers, labeled with the number of the run and subjected to different qualifications.

Table 1: Layout of the experimental 2^3 central composite design

Runs	Binder solution Conc. (%w/w)	Drying temperature (°C)	Drying duration (Hrs.)
Run 1	5	40	6
Run 2	20	40	6
Run 3	5	50	6
Run 4	20	50	6
Run 5	5	40	12
Run 6	20	40	12
Run 7	5	50	12
Run 8	20	50	12
Run 9	0	45	9
Run 10	25.1	45	9
Run 11	12.5	53.4	9
Run 12	12.5	53.4	9
Run 13	12.5	45	4
Run 14	12.5	45	14
Run 15	12.5	45	9
Run 16	12.5	45	9

Granules characterization

Collected granules from the first portion of all runs were scrutinized for the following specifications.

Bulk density

Granules were gently poured into pre-weighed 100 ml cylinder and the weight of the powder was measured using analytical balance (Reblab, Germany). The bulk density (BD) was then calculated as g/ml by dividing granules weight by 100 ml.

Tap density

Granules were gently poured into a pre-weighed 100 ml cylinder and then the weight of the powder was measured. The cylinder was then tapped against table at somewhat constant rate until no further decrease in the volume takes place, the tap density (TD) was then calculated as g/ml by dividing granules weight by the occupied volume.

Hausner ratio determination

To provide an excellent representation of uniformity in size and shape, deformability, surface area, cohesion, and moisture content, granules were investigated for determination of % compressibility using Carr index [8] where the ratio between tap and bulk densities for each granule run was estimated as H-ratio.

Particle size separation (% Fine)

Granules were subjected to particle size separation test by sieving through a nest of standard sieves ranging from 1700 to 425 µm mesh sizes on Automatic Sieve Shaker (D407, Italy). The weight of granules retained on the receiving pan was determined as the percent of the fine.

Granules assay

Weighed amount of granules equivalent to 0.06 gm of norfloxacin was crushed, transferred to 250 ml volumetric flask and dissolved in 200 ml phosphate buffer pH 4. The solution was then shaken for 2 min, sonicated for 20 min, completed to the volume with the phosphate buffer and filtered. 3 ml aliquot of the sample solution was transferred into 100 ml volumetric flask and diluted to the volume with the phosphate buffer pH 4. The absorbance of the samples was determined spectrophotometrically at 313 nm (double beam UV-1800 spectrophotometer, Shimadzu, Japan) against buffer as a blank. Making use of pre-conducted drug calibration curve, the amount of norfloxacin was then estimated. The assay method is derived from the USP norfloxacin tablets dissolution test monograph [9].

Validation of the analytical method

Validation of the UV spectrophotometric method for norfloxacin assay was ascertained by preparing 5 standard solutions of the drug (ranged 2.6-13.3 µg/ml) from stock solution of 240µg/ml norfloxacin in phosphate buffer pH 4. Absorbance of each concentration at 313 nm was determined spectrophotometrically in triplicate against buffer blank and calibration curve was thus generated. Solutions were analyzed within and between days. Precision, repeatability and reproducibility of the spectrophotometric method were established by calculating the recoveryn % and the relative standard deviations associated with repeatability (RSD_r) and reproducibility (RSD_R) [10].

Tablets characterization

Similar to granules, compressed tablets were also subjected to different tests as stated in the pharmacoepial general chapters and monographs [9] in order to determine their properties and quality.

Weight variation

Randomly selected 20 tablets from each run were weighed individually in an Analytical Balance (Reblab, Germany). The average tablet weight, standard deviation and the associated coefficient of variation were then calculated for each tablet run.

Tablets assay

10 randomly selected norfloxacin produced tablets were crushed using mortar and pestle and powder weight equivalent to 0.06 gm of norfloxacin was then processed for drug determination following the same procedure previously described with granules.

Friability test

Friability of the tablets was determined using 10 tablets. The weight of the tablets was taken before and after the cycling in the friability tester (Erweka, Germany) for 4 min in the speed of 25 rounds per minute and percent friability was obtained as the average % loss.

Hardness test

Hardness of 10 tablets from each run was measured individually using Tablet Hardness Tester (Caleva THT, China). The average hardness in Kg/cm^2 and the standard deviation were then calculated.

Disintegration test

The test was conducted in USP tablet disintegration tester (ZT3 Erweka, Germany) using purified water as disintegration medium at

37±0.5 °C. The average time required for randomly assigned 6 tablets from each run to disintegrate was determined.

Dissolution test

The dissolution of norfloxacin tablets was studied in USP dissolution test apparatus 2 (Erweka, Germany) operating at 50 rpm, using phosphate buffer 750 ml pH 4 as dissolution medium at 37±0.5 °C [9]. Six tablets were investigated at a time and samples were drawn at 30 min. 1 ml was drawn and transferred to a 50 ml volumetric flask and diluted with the phosphate buffer pH 4, filtered and absorbance was measured in duplicate for the six samples at 313 nm using phosphate buffer pH 4 as a blank solution. Making use of the generated calibration data, the percent of drug dissolved in 30 min was then calculated.

Statistical data analysis

Descriptive statistics were utilized for validation of the UV method of drug assay (standard deviation and coefficient of variation), predicting correlation coefficients for the drug determination from the standard calibration data (Pearson's r) and predicting regression coefficients associated with models' fitting processes. Moreover, inferential statistics relying on regression analysis, residual regression, surface model fitting, analysis of variance and mathematical approaches were used to examine the power of the individual and mutual influences of investigated variables on properties of granules and tablets. Computations were aided by software computer package STATISTICA 8 (Statsofts Inc., USA) and in all cases, probability $p \leq 0.05$ was considered as a cutoff point for significant influences.

RESULTS AND DISCUSSION

Calibration and UV method validation for norfloxacin content assay

Calibration plots for standard norfloxacin in solutions using the validated UV assay method show high acceptable linear correlation regression between drug concentration and UV absorbance with a highly established correlation coefficient (r = 0.9998, p = 0.0002) in the drug concentration range of 2—14µg/ml (fig. 1). As appears in table 2, values of relative standard deviation associated with method repeatability (RSD_r) and reproducibility (RSD_R) were ≤ 2% for a drug analyzed intra and between days. Moreover, displayed values of drug recovery for intraday and between days analysis for the three concentration levels were in the range 99.52-100.87% and 99.45-99.77%, respectively. The displaced values of % recovery, RSD_r and RSD_R assure the validity of the UV method for norfloxacin assay in granule formulations, tablet formulations and in dissolution samples with high precision, repeatability and reproducibility [10].

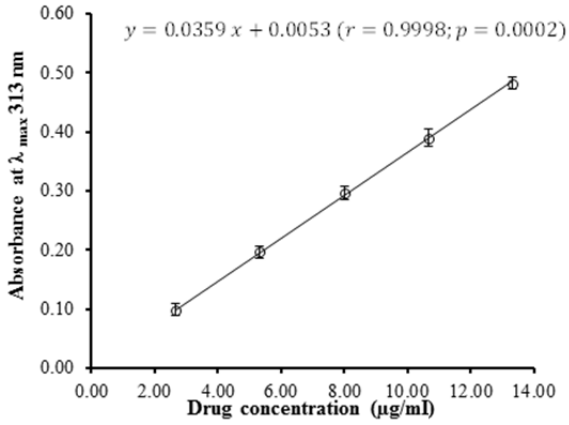


Fig. 1: Calibration plot for determination of norfloxacin in a solution using UV method. Each data point is the average of 3 determinations with error bars indicating±standard deviation (SD)

Table 2: Validation of the UV method for the assay of norfloxacin in granules, tablets and dissolution samples

Drug concentration level	N	% Recovery[a]	RSD_r	RSD_R
Intraday				
8.00 µg/ml	6	100.87%	0.169%	0.342%
10.66 µg/ml	6	99.52%	0.077%	0.253%
13.33 µg/ml	6	99.85%	0.331%	0.542%
Between days				
8.00 µg/ml	3	99.65%	0.235%	0.860%
10.66 µg/ml	3	99.45%	0.104%	0.933%
13.33 µg/ml	3	99.77%	0.376%	1.010%

N is a number of analysis replicates; [a]Accuracy in calculation of the concentration (obtained/actual *100%); RSD_r and RSD_R stand for relative standard deviation under repeatability and reproducibility conditions, respectively.

Table 3: Properties of granules within different formulation runs, values were presented as mean with respective standard deviation (SD) in parentheses

Runs	Bulk density (g/ml)	Tap density (g/ml)	Hausner ratio	% Fine*	Drug content (% w/w)
Run 1	0.344 (0.008)	0.521 (0.078)	1.5 (0.04)	86.00 (10.88)	89.14 (3.19)
Run 2	0.336 (0.007)	0.382 (0.082)	1.1 (0.02)	19.54 (3.89)	106.18 (4.33)
Run 3	0.331 (0.005)	0.493 (0.073)	1.5 (0.07)	67.33 (16.13)	96.82 (2.78)
Run 4	0.338 (0.010)	0.383 (0.088)	1.1 (0.01)	18.05 (6.39)	107.19 (4.61)
Run 5	0.334 (0.007)	0.491 (0.050)	1.5 (0.07)	54.72 (18.95)	102.84 (3.69)
Run 6	0.348 (0.004)	0.409 (0.064)	1.2 (0.02)	21.43 (3.51)	97.16 (2.51)
Run 7	0.328 (0.003)	0.490 (0.066)	1.5 (0.07)	74.18 (22.63)	106.52 (4.82)
Run 8	0.352 (0.013)	0.409 (0.072)	1.2 (0.04)	19.57 (6.69)	92.15 (2.58)
Run 9	0.391 (0.001)	0.584 (0.063)	1.4 (0.06)	88.68 (20.01)	91.48 (2.84)
Run10	0.320 (0.002)	0.381 (0.081)	1.2 (0.03)	21.35 (6.20)	99.16 (3.66)
Run11	0.342 (0.008)	0.445 (0.083)	1.3 (0.05)	28.60 (5.93)	87.80 (4.92)
Run12	0.327 (0.009)	0.431 (0.077)	1.3 (0.04)	30.48 (11.11)	102.84 (4.48)
Run13	0.307 (0.001)	0.432 (0.091)	1.4 (0.05)	32.42 (8.74)	103.84 (4.11)
Run14	0.324 (0.004)	0.463 (0.076)	1.4 (0.06)	44.38 (15.13)	104.18 (3.32)
Run15	0.329 (0.007)	0.427 (0.068)	1.3 (0.03)	31.50 (10.03)	110.53 (5.93)
Run16	0.330 (0.008)	0.422 (0.069)	1.3 (0.05)	32.34 (9.92)	102.17 (3.83)

*As estimated from fraction of granules<425 mm in diameter.

Influences of investigated variables on granules' properties

Properties of granules of different formulation runs are summarized in table 3 whereas individual (linear and quadratic) and mutual effects of binder solution concentration, drying temperature and drying duration on different granules properties are estimated in table 4.

Effects on granules' bulk and tap densities

The displayed average values for bulk density (BD) and tap density (TP) of different granule formulations are ranged 0.307-0.391g/ml and 0.381-0.584 g/ml, respectively (table 3). The observed variation in values within the two attributes is computed as trivial (p = 0.991and 0.982 for both properties, respectively).

None of the variables investigated in this study show an individual or influential joint effect on BD property of the produced granules (table 4). Although BD of the granules appears to increase with increasing drying duration, decreasing binder solution concentration or decreasing drying temperature as can be traced from the sign accompanying the estimated effects of variables in table 4, however, the consideration of these relations becomes high questionable in the light of the displayed large values of the probability accompanying each relation (p>0.05 for all relations).

Table 4: Effect estimates of investigated variables on the attributes of granules in different formulation runs

Variables setting	Bulk density	Tap density	H-ratio	% Fine	Drug content
BSC (L)	-0.001	-0.118*	-0.275*	-53.18*	1.744
BSC (Q)	1.064	3.658*	0.018	1660.63*	-379.80*
DT (L)	-0.003	-0.006	0.002	1.83	4.325
DT (Q)	0.327	0.585	-0.006	199.29	-310.13
DD (L)	0.008	0.013	0.009	0.48	-1.200
DD (Q)	-0.356	0.715	0.073	544.75	-73.307
Joint BSC and DT	0.017	0.020	-0.004	1.69	-4.149
Joint BSC and DD	0.015	0.027	0.027	6.48	-8.722*
Joint DT and DD	-0.003	-0.003	0.010	4.31	-1.893

BSC, DT and DD stand for binder solution concentration, drying temperature and drying duration, respectively; L and Q represent linear and quadratic level; * indicates significant effect with $p \leq 0.05$ at 95% confidence interval.

Generally, particle shape and diameter are known determinant factors for bulk density [11] and, consequently, it might be expected that at least concentration of binder solution as a variable should have an effect on densification of the granules [12]. Even so, it might be obvious that binder solution concentration, at the quadratic level, measures the highest influence on the bulk density of granules (1.064) as compared to the two other variables in this study (table 4), but such influence computed as inconsequential. This contradiction in findings might be attributed to the higher design of variable settings characterizing the present study.

With tap density property (TD), statistical estimates of effect encourage the consideration of binder solution concentration, as a variable, to have a profound influence on TD property of produced granules at both linear and quadratic levels (p = 0.0004 and 0.0013, respectively) as shown in table 4. At the interactive levels of variables and although none of the joint variable settings shows a significant influence on TD of the granules, yet, the result shows that the joint influence of binder solution concentration (BSC) and drying temperature (DT) in addition to that of BSC and drying duration (DD) are more influential on TD property of the granules than the individual effect of DT or DD as indicated by values of estimated effects (table 4). This, in turn, signifies the importance of consideration of the interactive influences that any couple of variables might have on attributes of these granule formulations.

As with BD, displayed result suggests that TD of the granules tend to increase with increasing drying duration, decreasing binder solution concentration or decreasing drying temperature. However, once more the validity of such suggestion remains uncertain based on the exhibited large p values of the three relations (p>0.05 for all relations).

In addition to determinant factors for BD, granule strength and % fine the powder contains are extra determinants for TD of granules and accordingly, it is expected that concentration of binder solution plays a major role in TD specification of granules as the result implies which could possibly be attributed to its direct influence on the two later determinants.

Effects on granules' Hausner ration and % fine

Because the inter-particulate interactions influencing the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder. Such a comparison is often used as an index of the ability of the powder to flow, for example, the Compressibility Index (CI) or the Hausner ratio (H-ratio) [8, 13].

As shown in table 3, demonstrated values for H ratio of the produced granules are significantly varied in the range 1.1 to 1.5 (p= 0.0026). In general, lower H-ratios of material indicate better flow properties than higher ones. An H ratio of<1.11 is considered excellent flow where H ratio > 1.60 is considered very poor flow. There are intermediate scales for H ratio including 1.12–1.18 for good flow, 1.19–1.25 indicating fair flow, 1.26–1.34 specifying passable flow, 1.35–1.45 designating poor flow, and 1.46–1.59 which representing very poor flow [8].

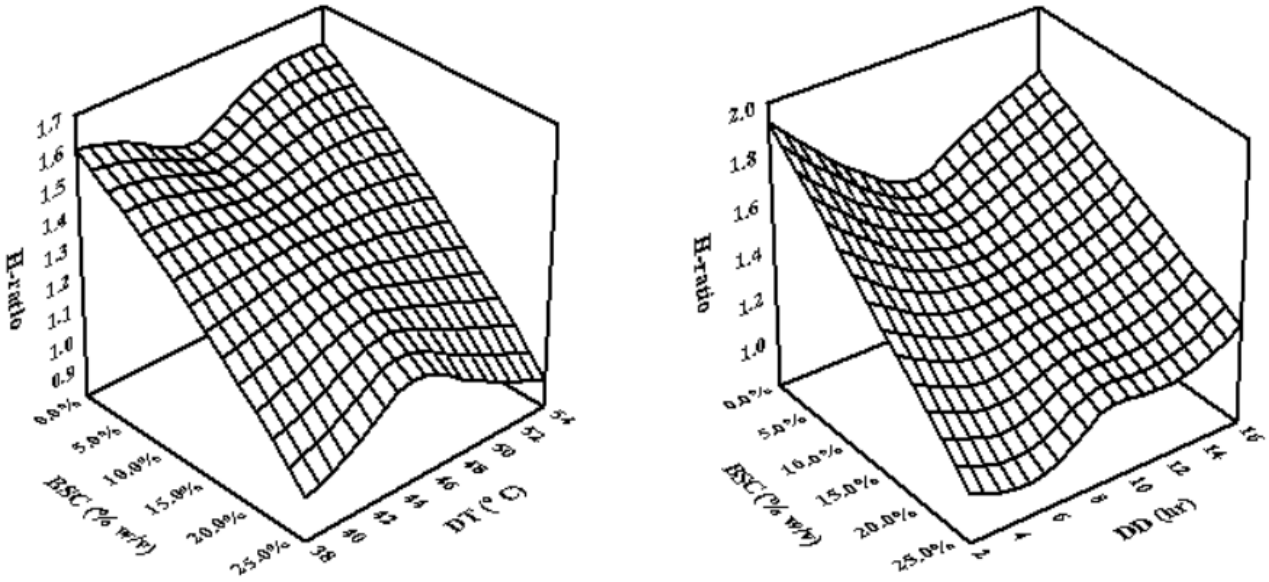
Among the three variables investigated in this study, only binder solution concentration confirmed to exert an effective linear impact on the value of H ratio (p= 0.0003; table 4) where H ratio tends to decrease with increasing the binder solution concentration regardless drying temperature and/or drying duration as illustrated in the surface plot concerning the combined influence of the three variables presented in fig. 2. Findings are in agree with a relevant published work [14] and could be explained in terms of the dependency of granule size on the quantity and feeding rate of granulating liquid which, in turn, determine flowability of powder or a granular blend. In other words, smaller granules tend to have greater cohesiveness due to high surface-to-mass ratio and result in greater bulk density. Therefore, the Hausner's index tends to increase with smaller granule size and the converse is also true.

From the displayed result in table 3 it is apparent that only 4 to 5 formulations out of the sixteen runs yield granules with free flow properties. However, no single test can characterize the granule flow effectively which is in agree with that stated by Yu, *et al.* [12].

Regarding % fine character of granules, values of % fine revealed by different granule runs are significantly varied (p= 0.002) between 18-89% (table 3). Percent fines means amount of powder remain in the granule, which, is necessary to avoid tablet cracks and to maintain effective tablet hardness during the process of tablet compression. % fine, however, should not be more than 30% and always a balance should be made between the mass of % fine that promotes tablet compression and that impedes free granules flow [15].

Similar to TD and H-ratio granule properties, BSC also appears as the sole variable that exhibits an influential linear and quadratic effects

among different variables examined (p= 0.0003 and 0.013, table 4). The result indicates that the curvature influence of BSC on the % fine of the granules is more profound than that of the linear effect. In both settings, however, the result encourages the assumption of a reverse relation between BSC and the % fine of granules (fig. 3), which might be attributed to the formation of larger agglomerates on increasing BSC as a consequence of providing more granules binding. These findings agree that of Singh *et al.* [16].



(a) **(b)**

Fig. 2: Surface plots for the combined influence of a) binder solution concentration (BSC) and drying temperature (DT), and b) binder solution concentration (BSC) and drying duration (DD) on Hausner ratio values of the granules in different runs

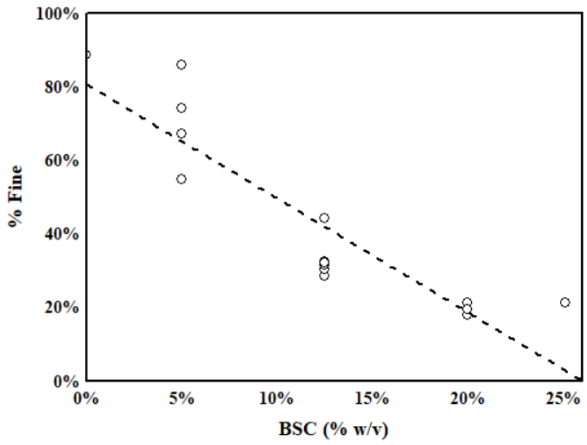


Fig. 3: Scatter plot for the individual effect of variation in binder solution concentration on fine % property of granules within different runs of the central composite design. Regression line describing the relation is shown on the plot

Effects on granules' drug content

Measured drug content among different granule formulations are broadly distributed in the range 87.8-110.5% (table 3) and such distribution verified to be statistically significant around the mean optimum value for drug content (p= 0.0004).

Binder solution concentration (at individual quadratic level) beside interactive linear level of binder solution concentration and drying duration both demonstrated to have a sizable effect on granules' drug content attribute (P = 0.039 and 0.045, respectively, table 4). Moreover, surface plot for the combined influence of BSC and DD on drug content attribute of the granules (fig. 4) provides an evidence for the association of the decreased drug content with increasing drying duration, in particular at high concentration of binder solution. Uniformity of drug content in solid dosage forms depends on the proper mixing and uniformity of flow; however, unlike the case with H-ratio, most of the granule formulations have satisfied the 100±5% criteria of drug content.

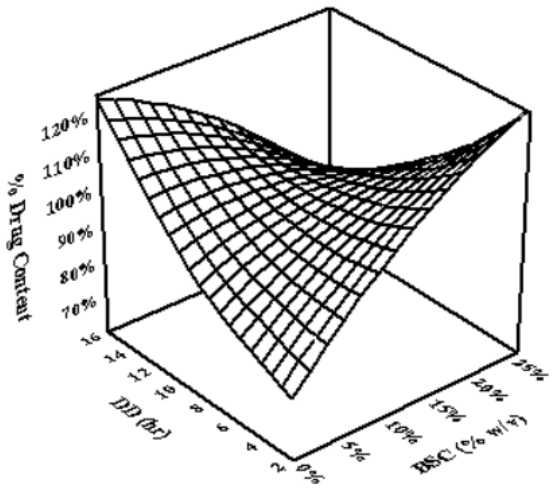


Fig. 4: Surface plot for the combined influence of binder solution concentration (BCS) and drying duration (DD) on drug content attribute of different granule runs

Influences of investigated variables on tablets' properties

Properties of different tablet runs are recapitulated in table 5 whilst influences associated with an individual (linear and quadratic) and mutual effects of binder solution concentration (BSC), drying temperature (DT) and drying duration (DD) on specification attributes of different tablet runs are summarized in table 6.

Effects on tablets' weight

The average tablet weight of within the sixteen formulation runs ranges 489.4-510.5 mg and such variation computed as insignificant (p = 0.403). As far as the values for tablet weight do not noteworthy varied from the hypothetical mean for tablet weight, it might be concluded that tablet weight property is within the acceptable range of compendia specifications for tablets.

Based on the values of the estimated effects of investigated variables, the results demonstrate some sort of association between different variables and tablet weight property (table 6). However, the strength of such association remains doubtful in the light of the displayed large values of probability term for significance (p>0.05 in all cases).

As variation in tablet weight may be related to inconsistency of granule flow, it should be noted that at least granules formulations exhibited H ratio>1.4 (run 1, 3 and 5) might be anticipated to demonstrate tablet weight variation due to non-uniform granules flow. Instead, the three runs yielded tablets with acceptable weight variation. This, in turn, supports that granules flow cannot be described by one variable as the literature tells.

Table 5: Properties of different tablet formulation runs, values represent the average measure (n = 20 for weight variation, n = 10 for % drug content, friability, and hardness, n = 6 for tablet disintegration and % drug dissolved)

Runs	Weight (mg)	% Drug content	Friability (%)	Hardness (kg/cm^2)	DGT[a] (min)	% Drug dissolved [b]
Run 1	493.1	101.8	1.0	2.8	0.5	91.8
Run 2	498.5	93.8	0.4	8.1	>15	80.3
Run 3	496.2	98.5	0.6	3.0	1	93.0
Run 4	501.4	98.2	1.2	2.7	7.3	95.0
Run 5	492.2	100.8	0.4	3.9	1	87.1
Run 6	507.9	88.5	0.7	6.8	>15	88.7
Run 7	498.8	95.2	0.6	3.1	1.3	95.0
Run 8	500.2	96.5	0.8	4.2	>15	49.0
Run 9	498.0	98.5	0.5	5.6	1.2	92.9
Run10	489.4	97.5	1.3	4.9	>15	77.2
Run11	490.5	98.5	1.0	2.7	5.3	98.1
Run12	501.4	100.8	0.5	3.8	6.5	104.9
Run13	497.2	98.8	1.1	2.3	4	94.4
Run14	498.5	98.8	0.9	2.7	6	91.8
Run15	510.5	90.8	1.5	2.5	5	102.3
Run16	505.8	100.8	2.4	1.9	6.8	95.50

[a]Tablet disintegration time and [b] as determined at 30 min.

Table 6: Effect estimates of investigated variables on the attributes of different tablet formulation runs

Variables setting	Weight	Drug content	Friability	Hardness	DGT	Drug dissolved
BSC (L)	1.972	-3.093	0.270	1.156	70.303*	-11.813
BSC (Q)	-8.059	0.314	-0.783*	2.510*	42.202*	-13.718
DT (L)	3.839	1.027	0.065	-1.174	-15.326	-0.508
DT (Q)	-6.756	1.518	-1.006*	1.377	12.743	-2.014
DD (L)	1.780	-1.667	-0.152	0.305	14.730	-6.585
DD (Q)	-5.071	0.890	-0.711*	0.530	8.650	-7.922
Joint BSC and DT	-3.625	5.325	0.275	-1.850	-23.625	-8.525
Joint BSC and DD	1.625	-0.675	0.125	-0.250	23.725	-8.725
Joint DT and DD	-1.775	0.325	-0.025	0.450	23.375	-11.925

BSC, DT and DD stand for binder solution concentration, drying temperature and drying duration, respectively; L and Q represent linear and quadratic level; DGT designates tablets disintegration time; * indicates significant effect with p≤0.05 at 95% confidence interval.

Effects on tablet's drug content

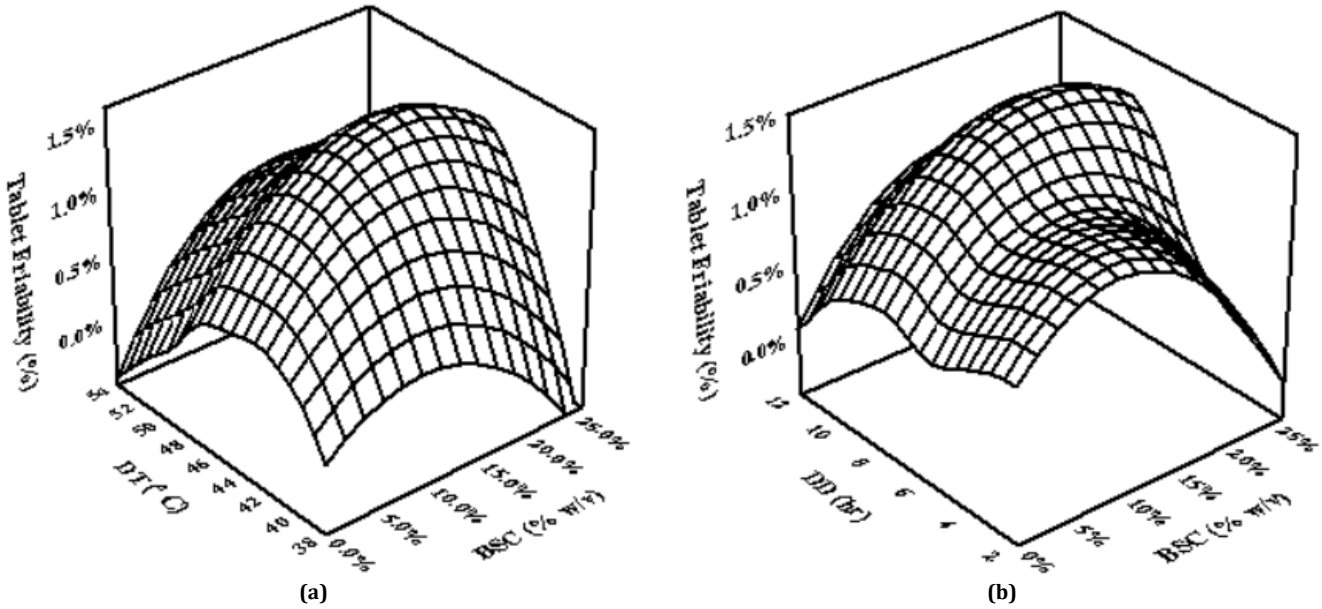
The displayed average tablets drug content for the sixteen formulation runs vary significantly in the range 88.5-101.8% (p = 0.011, table 5). None of the investigated variable measures a profound influence on tablets' drug content property at any variable setting (table 6).

The negative sign associated with effect estimates of BCS on tablets' drug content presumes a decrease in drug content with an increase in the binder solution concentration (table 6), which might be attributed to the incomplete of the granulation process where drug particles tend to concentrate in the granules of smaller size due to high viscosity of binder solution of increasing concentrations and, on the other hand, to the insolubility of the model drug Norfloxacin in the binder solution. This finding agreed that of Miyamoto, *et al.* [17]. Similarly, the results assume a decrease in tablets' drug content as a result of increasing the drying duration, DD, (table 6). Such assumption can be explained in terms of moisture and how it can affect powder flowability and since drying is a process in which liquid is lost by evaporation, the surface moisture of the granules wall eventually be exhausted as the drying proceed, resulting in a significant increase in cohesive strength and wall friction and, obviously, these effects are related to powder flow ability which is a known determinant for drug content variation in different solid dosage forms.

Effect on tablet's friability

Tablet formulations in the design measure friability that considerably varied in the range 0.4-2.4% (p = 0.009, table 5). All variables tested in this study reveal profound individual `influences on tablets friability through their quadratic setting (p<0.05 for these effects, table 6).

In other words, the pattern of the observed effects on tablet' friability exerted by either of BSC, DT or DD appear curvature in type rather than linear and, consequently, an increase in concentration of binder solution, drying temperature or drying duration are anticipated to be accompanied by an increase in tablet friability to a certain limit above which the influences become reversed where further increase in BSC, DT or DD would result in reduction of tablet friability, as can be shown in the surface plots for the combined influences of the three variables on tablet friability (fig. 5 a and b).



(a) (b)

Fig. 5: Surface plots for the combined influence of a) binder solution concentration (BSC) and drying temperature (DT), and b) binder solution concentration (BSC) and drying duration (DD) on tablet friability in different runs

It is known that increasing the concentration of binders to a critical limit would result in the formation of less friable granules and/or tablets. However, increasing the concentration of polyvinyl pyrrilidone (PVP, the binder used in the present study) beyond the critical limit might not lead to further growth of granules but rather widens the size distribution of the produced granules which, in turn, adversely affect the friability property. Findings are in accord with those concluded in many relevant works [18, 19].

On another hand, the observed quadratic influences of either DT or DD on tablet friability (fig. 5a and b) can be attributed to the rate and duration of granules drying and the consequent effects that both might have on bonding and strength characteristics of the dried granules. For a further investigation concerning the curvature type relation between tablets friability and either of DD or DT, a more detailed and fractionated designs seems necessary. However, extending the design into detailed or fractionated one is beyond the objectives of this study.

Effects on tablets' hardness

It could be true that crushing strength of the granules tends to increase as a consequence of increasing the concentration of the binder solution; however, this might not correlates with the tablets strength [19, 20]. The compression process results in a decrease in powder volume; owing to elastic and/or plastic deformation and the degree of particle attrition behaviors of the particle-particle bonds in the powder mass [21]. Table 5 shows values of the measured hardness of the produced tablets, which vary considerably in the range 1.9 to 8.1 kg/cm^2 ($p = 0.001$).

Among the three factors investigated in this study, only binder solution concentration confirmed to exert an effective quadratic effect on the tablet hardness ($p = 0.04$, table 6). Such effect suggests a decrease in tablet hardness with an increase in BSC up to specific border above which an increase of hardness is anticipated with further increase in BSC regardless the utilized drying temperature and/or drying duration, as illustrated by the fit plot for the observed polynomial influence of BSC on tablets' hardness (fig. 6).

The non-correlation between the strength of the granules and that of their produced tablets with the increase in binder concentration could possibly be attributed to the mechanism of granule formation and the formation of the binding bridges which cement the particle together [22]. Accordingly, the higher the concentration of the binder solution the harder will be the granules and the higher will be the compression force that needed for fragmentation and/or deformation to form compact formation. This finding is in agreement with that published by Nguyen *et al.* [20].

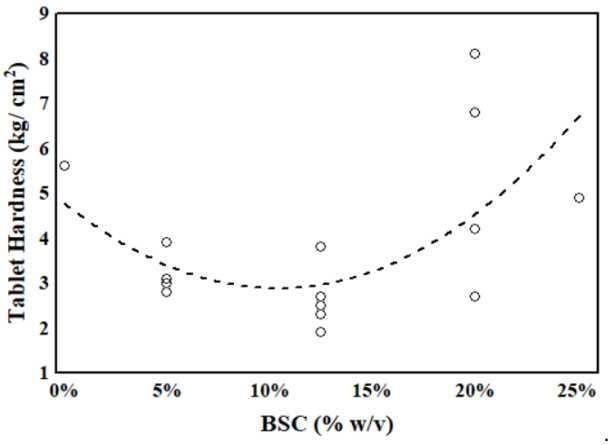


Fig. 6: Polynomial fit for the individual influence of binding solution concentration BSC on tablet hardness

On the other hand and as has been discussed under effects on granules' Hausner ratio and % fine, application of high binder solution concentration is associated with the production of granules of low % fine which might results in production of either fragile tablets or tablets of low hardness level as the result implies.

Based on known role of moisture content in tablet compressibility [23], the hygroscopic nature of the incorporated drug and excipients beside the effect of hemihydrates formation of Norfloxacin, it might be expected that DT and DD would measure profound influences on tablets' hardness. Yet, the result reveals minor and statistically insignificant influences of both variables on tablet hardness property at different setting (table 6) and, thus, encourages the ignorance of these influences, at least under the conditions of this study.

Worth mentioning that formulation runs measured low values of tablet hardness are those revealed high hardness levels (runs 2, 6 and 9, table 5) which, in turn, suggesting an inverse relation between tablet friability and hardness. In their co-authored work, Šantl., *et al.*

reported a reduction in tablet friability caused by increasing the applied compression pressure [24] and, moreover, compaction is related to particle consolidation and bonding which has a direct effect on the tablet hardness and friability [25].

Although the shown increase in tablet hardness in this study might not solely indicates an increase in the applied compression force, the findings could possibly be due to increasing granules intra-particulate bonding and tensile strength as a function of increasing binder solution concentration. Nevertheless, it can be estimated here that any variable that can increases tablet hardness can aid in decreasing tablet friability regardless of the binder solution concentration if the powder is characterized by good bonding properties as evidenced by tablets of formulation run 9 which incorporates no binder (table 1) and yet measures higher hardness when compared to those containing binder solution in concentration of 12.5%w/v (runs 11-16, table 1).

Effects on tablets' disintegration

The disintegration time of the tablets can be markedly affected by choice of excipients, production condition, and the applied punch force during tableting and the punch force-time relationship [21]. The disintegration time of tablets within different formulation runs varied in range 0.5->15 min (table 5). Among the three factors investigated in this study, only binder solution concentration was found to exert effective individual linear and quadratic influences on tablets' disintegration time ($p<0.05$, table 6).

The findings mean that BSC could exert linear influence in which utilization of increasing concentration of binder solution would result in tablets with increased disintegration time and, moreover, BSC could also have a non-linear (quadratic) influence on disintegration time where initially the disintegration time appears less sensitive to variation in BSC up to specific boundary beyond which a proportional prolongation in disintegration time with further increasing of BSC becomes apparent (fig. 7). Nevertheless, the ultimate retardation of tablet disintegration with increased BSC is apparent with both influences.

The prolongation in tablets' disintegration time that observed with increasing BSC is attributed to the increasing binding capacities of the granulating agents at higher concentration. Therefore, the amount of binder in a given formula will be a compromise between desired granule strength and desired disintegration time, as reported earlier [26].

Although DT and DD show varying effects on tablets' disintegration time, the decision concerning the significance of their influences remains the same as that on tablet hardness owing to the relative high values of the probability (P) associated with their influences ($p>0.05$ for both influences).

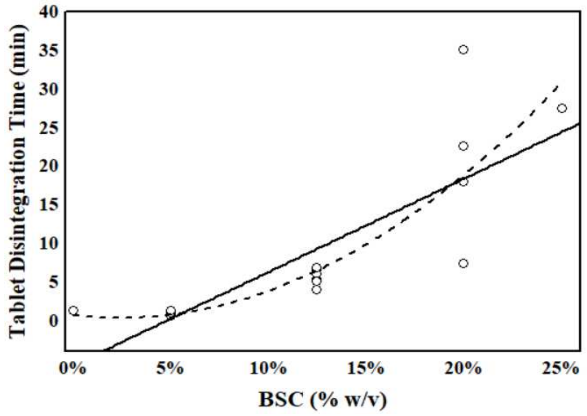


Fig. 6: Linear (solid line) and polynomial fit (dotted line) for the linear and individual quadratic influence of binding solution concentration BSC on tablets' disintegration time

Effect on tablet's drug dissolution

The mean % drug dissolved at 30 min of different tablet formulations vary noticeably between 49 and 104.9% (P = 0.005, table 5).

BSC, DT and DD proved to exert inconsequential influences on drug dissolution attribute of the tested tablet formulations as denoted by values of probability for significance term, p, associated with all possible settings of the three variables ($P>0.05$ for all settings, table 6).

Despite the statistical ignorance of the influences of BSC and DD on % drug dissolved at 30 min, changing profiles of drug dissolution as a consequence of varying BSC and DD (fig. 7a and b, respectively) encourage the consideration of retarding influences of both variables on drug dissolution property. Yet, validation of such relation is ambiguous and difficult to verified, at least under this study conditions.

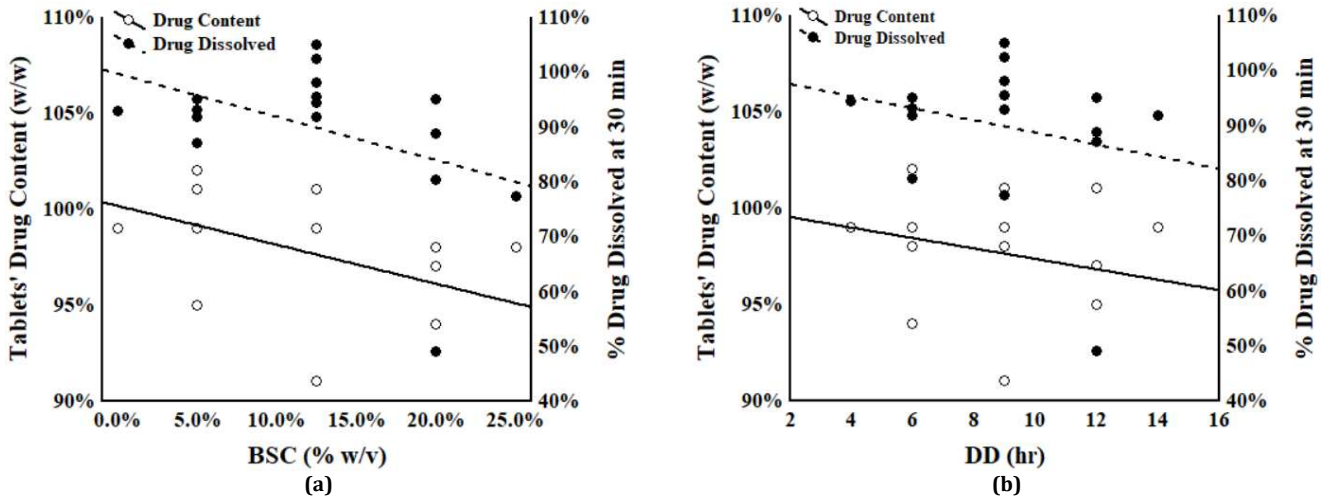


Fig. 7: Variation of tablets' drug content and drug dissolution patterns in the design runs as a consequence of changing the setting values of a) Binder solution concentration (BSC) and b) Drying duration (DD)

An interesting finding is the correlation pattern between % drug content and % drug dissolve at 30 min that shown in fig. 7a and b. This finding supports the explanation derived before which attributed the decrease in % drug content to the loss of smaller granules loaded with the drug as a result of the enhanced proportion of % fine, especially as the binder solution concentration increases.

Based on the pharmacoepial acceptance criteria for drug dissolution [9], only two runs out of the sixteen runs (runs 8 and 10) fail to meet the dissolution specifications (table 5). In some instances, failure to meet dissolution criteria might be attributed the high hardness level of tablet formulations [21], however, it is not the case here as some tablet formulations in this design measure comparative high hardness levels (runs 2 and 6, table 5) and yet have met the drug dissolution criteria.

As a matter of fact, drug dissolution failure of run 8 and 10 better to be explained in terms of the delayed disintegration time of the two formulation runs where tablets of both runs measured>15 min for their disintegration. Moreover, tablet runs showed disintegration time of 1-8 min were capable to release ≥ 90% of the loaded drug within 30 min, with an exception to run 5 (table 5). In most pharmaceutical technology operations it is difficult to alter one process without adversely affecting another one, for example, increasing compression pressure to produce stronger tablets may also impair disintegration and prolong dissolution.

CONCLUSION

The study put assertion on the influences that formulation and processing variables (binder solution concentration, drying temperature and drying duration) could have on the attributes and performance of produced Norfloxacin granules and tablets. Compared to drying temperature and drying duration, binder solution concentration exhibited more profound influences on tap density, H-ratio, % fine and drug content attributes of granules either through its individual linear and quadratic effects or through its joint effect with drying durations. Binder solution concentration, drying temperature and drying duration found to exert considerable quadratic influences on tablet friability, whereas substantial linear or quadratic influences on tablets' hardness and disintegration were observed only with binder solution concentration. Among different tablet properties, drug content, drug dissolution and tablet weight measure no response to setting variation in any of the three investigated variables. The study highlights the importance of consideration of quadratic and joint influences of variables in screening designs.

AUTHORS CONTRIBUTIONS

Authors of this manuscript share an equal contribution in all steps up to the approval of the final version.

CONFLICTS OF INTERESTS

The authors declare that they have no competing interests

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